Blinding, Control Groups, Placebos, and Behavioral Trials

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Objectives

- To understand the benefits of
  - Blinding
  - Control Groups
  - Placebo
  - Behavioral placebo

  for reducing bias

Definition of Bias

- Webster's New Collegiate Dictionary
- 2 a: an inclination of temperament or outlook; *esp*: a highly personal and unreasoned distortion of judgment: prejudice <a bias in favor of jolly fat men>
- 2 c (1): deviation of the expected value of a statistical estimate from the quantity it estimates (2): systematic error introduced into sampling or testing by selecting or encouraging one outcome or answer over others

Unblinded Trials

- Also called an open trial
- Sometimes the only option
  - Surgical trials
  - Comparison of devices/medical treatment
  - Changes in lifestyle
- Easier to perform
- May reflect practice better

Unblinded Trials, Cont.

- Susceptible to bias
  - Reporting of symptoms and side effects
  - Prescription of concomitant or compensatory treatment
  - Dissatisfaction with treatment and dropout
- "…preconceived notions about the benefit of a treatment, coupled with a subjective response variable, may have yielded biased reporting" – Friedman, Furberg, DeMets
- Often some aspect can be blinded (e.g., evaluation)

Types of Blinded Studies

- Single-Blind: patient does not know which treatment she receives
- Double-Blind: neither participants nor investigators know which treatment is received
- Triple-Blind: DSMB (and sometimes the statistician) see results only by group (A and B)

Single-Blinded Studies

- Can eliminate patient influences on outcome
- Easier to conduct than are double-blinded studies
- Investigators can exercise their best judgment when caring for participants
- Data collection, administration of non-study therapy are subject to bias

Single-Blinded Studies, Cont.

- Assume that investigators:
  - believe active treatment is superior
  - want all of their patients to do well
- Can lead to group differences in concomitant and compensatory treatment
- Concomitant therapy (non-study) medication can increase variability even if there are no group differences
- Compensatory treatment (either additional advice or therapy) can cause biases
  - Possible reduction of group differences
  - Or could want to “prove” treatment is effective

Double-Blinded Studies

- Usually restricted to trials of drug *efficacy* (what the drug does in an ideal setting)
- Risk of bias is reduced
- More difficult to conduct
  - DSMB may be needed
  - Additional personnel needed as investigator cannot know treatment assignment
- Investigators are often uncomfortable with double-blinded studies because they relinquish control and don't know what is happening

Triple-Blinded Studies

- Groups are A and B
- Monitoring committee can monitor results more objectively
- Often decision to continue depends on which direction.
  - Want to prove active treatment is better
  - Don’t care as much about proving placebo is better
- Can start out with a blinded DSMB which can ask to be unblinded if it would impact decision
- Be careful—DSMB story of 2 active drugs

Blinding of Statisticians

- Rarely done
- Groups could be assigned A and B by a programmer
- Example: Dog study at Searle in the early 1990s
  - Dogs identified by name
  - Wouldn't give statistician the name of one—"Wolf"—for fear of bias
  - Aside: Most widely used Searle product???

Unblinding

- Sometimes medically necessary (ED visit)
  - Needs to be always available
  - Patient and investigator don't necessarily have to be unblinded
  - Patient can sometimes simply stop meds
- Use of signs to remind participants not to unblind evaluators in open label studies with blinded evaluation
- Side effect profile may effectively unblind

Statisticians and Unblinding

- It takes time to ensure in large multi-center trials
- No laboratory data that would unblind
  - E.g., serum calcium or vitamin D levels in a blinded, placebo-controlled trial of calcium and Vitamin D on bone mass
- No post-baseline analysis to investigators
- Investigators hate this because they aren't sure what is happening…nag, nag, nag!
- Response: DSMB voted to continue study.

Assessment of Blindness

- Ask participants/investigators/staff which treatment a participant received
- Expect 50% accuracy for both active and placebo if blinding was successful, 100% if completely unblinded
- Expect accuracy to be equal between active and placebo if blinding was successful

Control Groups

- Need to make a comparison—have to compare to something
- The control group should be similar in all respects to the active group—achieved through randomization
- Often compare a new treatment to an existing, established, treatment
- Often there is no alternative that has been proven effective—Use a “placebo”

Onerous Control

- Many years ago I reviewed a GCRC protocol involving brain stents
- The investigators proposed subjecting the control group to open-brain surgery with an expected 8% risk of *major brain infection*
- It was not approved
- Controls cannot be unethical

Definition of Placebo

- Webster's New Collegiate Dictionary
- 1: the Roman Catholic vespers for the dead
- 2 a (1): a medication prescribed more for the mental relief of the patient than for its actual effect on his disorder
- 2 a (2): an inert or innocuous substance used esp. in controlled experiments testing the efficacy of another substance (as a drug)
- 2 b: something tending to soothe

Use of Placebo

- Ethical if
  - There is no standard intervention clearly superior to placebo
  - Participants should fully understand their chance of receiving placebo
  - Other circumstances (e.g., commonly used therapy not well tolerated)
- Clinical Equipoise—"presence of uncertainty as to the benefits or harm from an intervention among the expert medical community, rather than the investigator, is justification for a clinical trial"
- "In all trials, there is the ethical obligation to allow the best standard of care to be used."

Design of Placebo

- Commonly used in drug studies
- Participants and investigators are curious
- Active and placebo must match
  - Taste, odor, size, weight, specific gravity of pills
  - Labels, bottles, coding
  - Addition of dyes or flavoring to mask differences or prevent tasting

Placebo Effects

- Possible Definitions of Placebo Effect
  - Before-after difference in placebo group (temporal-less useful)
  - Effect of placebo intervention (causal)
    - Estimate the difference between placebo and no-treatment in randomized trials
  - Patient-provider interaction
    - Compare manipulation of the patient-provider interaction with no manipulation
  - Neither can be double-blinded
- Hróbjartsson, 2002

Types of Bias in Behavioral Trials

- Investigator Bias
  - Use multiple therapists and analyze for therapist effect
  - use independent blinded evaluators
  - Have therapists deliver both interventions
- Patient Expectation (Placebo Response)
  - Control group treatment should be plausible to patients (measure credibility)
  - the control should not have a significant impact on the hypothesized mechanism of action
  - Whitehead has used two consent forms—difficult to implement
- Whitehead, 2004

Types of Bias in Behavioral Trials, Cont.

- Ascertainment Bias
  - Self Selection
    - Subjects often want active arm
  - Differential dropout
    - More people drop out of control arms than active treatment arms
- Nonspecific effects
  - Doctor-patient relationship
    - Placebo response is greater when physician meets with patient
  - Regression to the mean (natural history of the disease)
    - chronic disorders can vary over time and patients are more likely to seek treatment (enroll in trials) when they are at their worst
- Whitehead, 2004

Problems with Behavioral Control

- “It is not possible to blind the investigator as to which treatment the patient is assigned and whether it is the active treatment or the control treatment”
- “It is difficult to identify a control intervention that is inactive but equally credible”
- “Doctor-patient relationship variables are more important in behavioral trials”
- Whitehead, 2004

Behavioral Control

- Control treatment should:
  - be plausible
  - the control should not have a significant impact on the hypothesized mechanism of action
- Whitehead, 2004

β-Blocker Heart Attack Trial

- Placebo-controlled trial of propranolol hydrochloride on mortality
- 79.9% of patients receiving active thought they were on active
- 57.2% on placebo thought they were on active
- Physicians: 69.9% correct for active, 68.8% for placebo
- Coordinators: 67.1% correct for active, 70.6% for placebo
- Propranolol reduces heart rate, thought to be reason for unblinding
- Byington, 1985

Vitamin C for Common Cold

- Does Vitamin C work as a prophylactic or therapeutic agent for the common cold?
- 311 NIH employees recruited
- 4 arms in a 2-by-2 design
- Maintenance: 3 grams Vitamin C vs. placebo
- Supplement: 3 grams Vitamin C vs. placebo

Vitamin C, Cont.

- Study stopped at 9 months
- Investigators were aware that some were tasting pills
- More placebo participants dropped out (P=0.1)
- Post-study questionnaire:
  - 76.9% on Vitamin C suspected Vitamin C
  - 22% on placebo suspected Vitamin C
  - P<0.001

Vitamin C, Cont.

- Prevention:
  - 1.27 colds/9 months for Vitamin C
  - 1.36 colds/9 months for Placebo
  - P>0.5
- Treatment:
  - 7.24 day duration for placebo
  - 6.59 day duration for 3 g Vitamin C (2 groups)
  - 5.92 day duration for 6 g Vitamin C

Vitamin C, Cont.

- “Thus, each 3-gm increment of ascorbic acid would appear to shorten the mean duration of a cold by approximately half a day. However, these differences were eliminated by taking into account the correct guesses of medication ingested.”

Duration of Colds (days) for “Blinded Subjects”		
	Mainten-ance	
Supple-ment	0 g	3 g
0 g	6.3	6.4
3 g	6.7	6.5

Vitamin C, Cont.

- “There was no time to design, test, and have manufactured a placebo that would be indistinguishable from ascorbic acid. It did not occur to the investigators that a substantial number of the volunteers, presumably fully informed about the purpose of the study and the importance of the double blind, would not be able to resist indefinitely the temptation to learn which medication they were taking.”
- Karlowski, 1975

Summary

- Reduction of bias
- Blinding
- Controls
- Behavioral Placebo
  - Should be plausible
  - Should not impact mechanism of action

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Statistics Joke

- No such thing???
- Statistics books are somewhat dry
- Occasionally a good (usually unintentional) pun can be found. Some are truly awful.
- Success runs in Bernoulli trials. For example, a basketball player makes 10 free throws in a row.